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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/765,012	12/19/96	WILD H	BAYER9776-K

EXAMINER

HM31/0401

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DRAPER, G

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 04/01/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-2 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☐ Claim(s) _____ is/are rejected.
☒ Claim(s) 1-2 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5 & 6-26-97
☒ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

Part III: Detailed Office Action

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Group 1640 Technology Center 1600.

2. Formal Matters:

2a. The reply filed 9-30-97 is not fully responsive to the communication mailed 5-23-97 for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report.

Since the above-mentioned reply appears to be *bona fide*, applicant is given a TIME PERIOD of **ONE (1) MONTH** or **THIRTY (30) DAYS**, from the mailing date of this notice, whichever is longer, within which to supply the omission or correction in order to avoid abandonment. EXTENSIONS OF THIS TIME LIMIT MAY BE GRANTED UNDER 37 CFR 1.136(a).

It is pointed out that applicants have made a bona-fide attempt to comply with the Sequence Rules, but such compliance appears to have been restricted to that for the probes at pages 6, 17-18. However, at pages 5 and 9 there are 9 and 4 partial amino acid sequences, respectively, that have 4 or more amino acid residues. According to 37 CFR 1.1821(a) there must be compliance for these sequences (see PEP 2422.01). The fact that these partial sequences have parentheticals dispersed between them to identify the residue number does not preclude these sequence from the requirement for sequence compliance according to the rules.

2b. The disclosure is objected to because of the following informalities:

--The periods "." used in the recitation of the US patents at page 3 and throughout the specification should be changed to commas ",".

-- The "cf" abbreviation at page 9 should be corrected .

Appropriate correction is required.

2c. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
© Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(I) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

The specification should be amended for such headings as stated above, and this is especially true for a "Brief Description of the Drawings".

2d. The Examiner appreciates the extensive nature of the relevance of documents cited on the PTO 1449, and that applicants pointed out, where in the specification, the citations appeared.

3. This application was filed under 35 UC 371, thus all claims will be examined herein.

4. Double Patenting Rejections:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4a. Claims 1-2 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,723,118. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope with regard to modifications made at residues 121, 124 add/or 125 either alone, or in combination with other modifications on the Il-4, irrespective of the fact that the mutants may be referred to by different names, and irrespective of the recitation of additional properties/characteristics or intended uses.

4b. Claims 1-2 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-22 and 25 of copending Application No. 08/897~~202~~920. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope with regard to modifications made at residues 121, 124 and /or 125 either alone, or in combination with other modifications on the Il-4, irrespective of the fact that the mutants may be referred to by different names, and irrespective of the recitation of additional properties/characteristics or intended uses.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4c. Claims 1-2 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 08/874697. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope with regard to modifications made at residues 121, 124 and/or 125 either alone, or in combination with other modifications on the Il-4, irrespective of the fact that the mutants may be referred to by different names, and irrespective of the recitation of additional properties/characteristics or intended uses.

This is a provisional obviousness-type double patenting rejection because the conflicting

claims have not in fact been patented.

4d. Claims 1-2 rejected under 35 U.S.C. 103(a) as being obvious over Sebald.

The applied reference has a common Assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application of any unclaimed subject matter prior to the effective U.S. filing date of the reference under 37 CFR 1.131.

The claims overlap in scope with regard to modifications made at residues 121, 124 and/or 125 either alone, or in combination with other modifications on the Il-4, irrespective of the fact that the mutants may be referred to by different names, and irrespective of the recitation of additional properties/characteristics or intended uses.

5. Objections and Rejections under 35 U.S.C. §112:

The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

5a. Claim 2 is objected to because of the following informalities: Similar to the previous paragraph, claim 2 is not further limiting in the preamble recitation to a "medicament", because the claim fails to recite any other features/limitations to distinguish the claim. Thus, the claim is objected to as being a duplicate of claims 1, despite slight differences in the wording and in view of a different preamble recitation (See MPEP 706.03(k). Appropriate correction is required.

Applicant is advised that should claim 1 be found allowable, claim 2 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Amending claims 2 in a similar manner would obviate this rejection:
"A therapeutic composition comprising the human IL-4 mutants of claim 1 and a pharmaceutically acceptable carrier"

In view of the format to claim 1, particularly relative to the various recitations of "and/or", it is not clear what the individual scope is for these various potential alternatives, nor what the full scope and intent of these claims are. Thus, in view of a reasonable interpretation of the intent and scope, the following rejections are applied. However, it is strongly suggested that the claims be amended (similar to the above suggestion for claim 2) to use more conventional U.S., claim's language. Furthermore, it is suggested that applicants present dependent claims to address some of these alternative embodiments-particularly for: a) modifications at glycosylation sites: b) to polymer conjugates such as PEG conjugates-each of which are distinctly different form the mutants per se.

5b. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of Il-4 mutants wherein certain modifications are made at residues 121, 124, and 125 alone or as combined with a limited number of other modifications, does not reasonably provide enablement for all modifications at residues 121, 124 and 125 in conjunctions with all other possible modifications (inclusive of insertions/substitutions, deletions and additions) throughout the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use, with a reasonable expectation of success, the invention commensurate in scope with these claims.

The specification has provided enablement for some of the IL-4 mutants that would be considered agonist and/or partial antagonist that fall within the scope of the claims; however, the limited number of examples, the evidence, guidance and teachings set forth in the specification are not commensurate with the breadth of the claims. While it is well settled that a specification need not contain examples in order to be enabling, in the express absence of such, the specification must provide enablement alternatively in the form of evidence or guidance. It is also known and accepted that examples, evidence of guidance are not required if, on its face, it is clear to the

skilled artisan that the claims are enabled; and when there is no reason to question the objective truths of applicant's mere statement of assertions that modifications can be made at residues 121, 124 & 125 alone or in conjunction with all other medications at the N- or C-terminus of Il-4 are properly with the scope of the claims. However, in addition to there being insufficient examples, the specification is also devoid of sufficient evidence or guidance that would serve to enable the scope of the claims. The following discussion will serve to establish the Examiner's position for questioning the objective truth of applicants mere statements, and consequently show that these claim limitations are not enabled by the specification.

For example, applicants concede at page 13 of the specification that "it is difficult to predict the properties of an Il-4 variant", but further conclude that screening of these variants, by state of the art methods, is required in order to achieve the optimum variants. However, it is the examiner's position that while the general nature of some of these methods may be state of the art, they, in and of themselves, are not sufficient to enable the full scope of the claims. What is taught in the specification is that residues 121, 124 and/or 125 can be mutated to Arg, Tyr or Ser; and the examiner concedes that modifications at glycosylation sites are well known and established in the art. However, the modification at these sites with any one of the other amino acids, which may or may not represent conservative substitution alone or in combinations with other mutations at the C- or N-terminus, in order to produce Il-4 mutants that are either agonist or partial antagonist, has not been enabled by the other teachings in the specification, nor are they predictable from the expressly taught mutations as stated above. Applicants have only referred to alanine-scanning mutagenesis and general procedures for making protein modifications that represent "boiler-plates" for mutagenesis techniques (see pg 7-9), but has failed to provide any **evidence or guidance** as to how one would go about picking and choosing the appropriate residue that could be mutated by these procedures with reasonable assurance that the resultant mutants will possess the desired activity. Furthermore, the skilled artisan would have to be knowledgeable of structure/functions studies on the protein and which regions where the desired activity resides (such as the various activities listed at page 13 of the specification) in order to

selectively determine which residue(s) can be mutated to produce and agonist or antagonist. It is this information that has not been provided or enabled by the specification, and in the express absence of such, to enable the full scope of the claims would constitute undue experimentation.

Furthermore, while the specification has taught that residues 121, 124 & 125 can be substituted with certain residues, the claims broadly encompass additional "modifications" that could be additions or deletions mutations, which also have not been enabled for these claims. In addition to this, the claims refer to these modifications at the N- or C-terminus, but it is not clear; nor has the specification enabled whether this is the very terminal residues, or if this constitute multiple residues at these termini and how many of these terminal residues are modified.

Further supportive of the fact that the full scope of the claims constitute undue experimentation, it is pointed out that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structural/ functional relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding, stability, or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for sites which represent other characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity. These various regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990. Science, Vol. 247, pp.1306-1310, especially p.1306, column 2, paragraph 2; and see Ngo et al, The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz er (ed.), pages 433 & 492-495, and Frommet et al/1985). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to

change (e.g. such as by amino acid substitutions, insertions or deletions), and the nature and extent of the changes that can be made in these positions in order to obtain multiply-mutated proteins. Such extensive modifications might also read on previously characterized proteins; alternatively, this might also include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See Ex parte Forman, 230 U.S.P.Q. 546 (BPAI 1986) with regard to the issue raised above and In re Fisher, 166 USPQ 18.

Further, the cited portion of the specification only sets forth art-recognized and generic procedures for obtaining the various mutated proteins, and therefore is not adequate guidance for the vast number of mutants that are encompassed by the claims, but is rather a mere invitation to the artisan to use the current invention as a starting point for further experimentation. The scope of applicant's claims encompass modification on the protein that would be critical as well as non-critical for the biological activity of the protein. Thus, even if **critical** residues were identified, which in this case they are not, the mere identification of these critical regions would not be sufficient as the ordinary artisan would immediately recognize that the modified site must assume the proper three-dimensional configuration to be active-which conformation is dependent upon surrounding residues. Even the substitution/insertion/deletion of non-essential residues can often destroy activity, therefore, it is deemed that to make each of the possible amino acid modifications for each of the non-essential residues, even if only conservative replacements were made, would also constitute undue experimentation. The introduction of non-conservative substitution, non-naturally occurring amino acids, deletions or insertions further raises the possible number of species. Therefore Applicant has not presented enablement commensurate in scope with the claims.

6. Rejections Over Prior Art:

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point

out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6a. Claims 1-2 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tony et al or Kruse et al (Ref AA, AI or AJ).

Each of the prior art disclose Il-4 mutants, wherein the modifications have been made at residues 121, 124 or 125, or wherein additional modifications have been made on the protein, which meet the limitation of the claims for single or multiple mutations on the Il-4 (see the abstracts and results/tables or each). Also taught is that these modification cause the Il-4 to have agonist or antagonist activity. In light of the various alternatives in which the claims are directed for Il-4 mutants, these prior art appear to anticipate the claims. Although the prior art do not expressly state that the mutants are medicaments, in view of the fact that such modification were made with the express purpose of obtain modified forms of the protein that could be use in therapy of diagnostic, the limitation of claim 2 appears to also have been made by the prior art-especially since claim 2 does not recite any of elements to distinguish it over the mutant per se as recited in claim 1.

6b. Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Tony et al or Kruse et al (AA, AI, or AJ) in view of Anderson et al or Francis.

The disclosure of each of the primary references has been set forth above, but not specifically taught by each of these primary reference is the modification of Il-4 at glycosylation sites, or the conjugation of the IL-4 mutants to polymers such as PEG. Anderson et al teach that Il-4 can be mutated as glycosylation sites (see the claims). Francis teach that protein can be conjugated with PEG to increase their half-life (see all). No one prior art individually disclose each aspect of the invention, however, at the time of the invention it would have been prima facie obvious to take the Il-4 mutants of the primary reference and make further modification on them at glycosylation sites, as taught by Anderson et al, in order to achieve the combined effect of such modification, because Anderson et al taught that such modification are advantageous to inactivate the glycoslyation site for expression purposes or for binding of the carbohydrate to the membrane, which the art had also established would cause immunogenicity problems and reduce the bioavailibility of a protein.

Likewise, it would have also been prima facie obvious to take the Il-4 mutants of the primary reference and conjugate them to polymers such as PEG, as taught by Francis, in order to obtain Il-4 mutants that possess and increase in their half-life, because Francis taught that this is a desired advantage for protein where there is a desire to use them therapeutically.

7. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. **This is applicable to any intervening art.**

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The other art listed on the PTO 892 is cited as of interest.

9. Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to **Garnette D. Draper, Art Unit 1646, whose telephone number is (703) 308-4232.** Examiner Draper can normally be reached Monday through Friday, 9:30 A.M. to

6:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

GARNETTE D. DRAPER
PRIMARY EXAMINER
GROUP 1800